Mini-Review

Prevention of Hepatocellular Carcinoma

Kerstin Schütte^b Fathi Balbisi^a Peter Malfertheiner^a

^aDepartment of Gastroenterology, Hepatology and Infectious Diseases, Otto von Guericke University of Magdeburg, Magdeburg, and ^bDepartment of Internal Medicine and Gastroenterology, Niels-Stensen-Kliniken, Marienhospital Osnabrück, Osnabrück, Germany

Key Words

Hepatitis B virus · Hepatitis C virus · Hepatocellular carcinoma · Nonalcoholic fatty liver disease · Nonalcoholic steatohepatitis · Prevention

Abstract

The epidemiology of hepatocellular carcinoma (HCC) has significantly changed throughout the past decade and will continue to do so in the future as a consequence of effective primary prevention and treatment of virus-related liver diseases. However, other risk factors for HCC are constantly on the rise, including alcoholic liver disease and nonalcoholic fatty liver disease. The knowledge on these and further risk factors associated with an increased risk of HCC provide the opportunity and chance for the development and implementation of successful preventive strategies to decrease the worldwide burden of HCC. This mini-review gives a short overview on current strategies in primary, secondary, and tertiary prevention of HCC.

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Introduction

The incidence of hepatocellular carcinoma (HCC) is still on the rise with 782,000 new cancer cases having occurred worldwide in 2012 [1]. More than 80% of the liver cancer cases were diagnosed in less developed regions of the world. Liver cancer is still the second most common cause of death from cancer worldwide, and is estimated to be responsible for nearly 746,000 deaths in 2012. Chronic liver diseases are the most significant risk factor for HCC development. The incidence varies among geographical regions mostly and is influenced by the distribution of the major etiological factors [2]. The majority of cases develops in the setting of chronic liver inflammation that progressed to liver fibrosis or cirrhosis which is the

Prof. Dr. med. Dres. h.c. Peter Malfertheiner
Department of Gastroenterology, Hepatology and Infectious Diseases
Otto von Guericke University of Magdeburg
Leipziger Strasse 44, DE-39120 Magdeburg (Germany)
E-Mail peter.malfertheiner@med.ovgu.de

major risk factor in 70–90% of patients [2]. About 75% of cases are related to chronic virus-induced hepatitis, with hepatitis B virus (HBV) infection being the predominant risk factor worldwide. Other leading risk factors for HCC include, amongst others, hepatitis C virus (HCV) infection, contamination of food with aflatoxin, alcohol-induced liver disease (ALD), and nonalcoholic steatohepatitis (NASH). The interventions on the prevalence of some of these risk factors, including HBV immunization programs, successful treatments of HCV infection, and reduction of aflatoxin food contamination, have already resulted in significant changes in the epidemiology of HCC. Notably, there is a decrease of infection-related cases but an increase in cases related to other risk factors, with NASH being the predominant factor [3]. For younger patients, HCC results in the loss of a considerable number of years-of-life with an estimated lifespan loss of 19.1 years shown in a recent study [4]. The knowledge about risk factors for HCC provides the opportunity and chance for the development and implementation of preventative strategies aiming at an efficient and effective prevention of HCC to decrease the worldwide burden of the disease [5]. Primary prevention focuses on risk factors for HCC and their treatment at an early stage, secondary prevention concentrates on the treatment of underlying liver diseases in patients with HCC aiming at a prevention of disease progression, and tertiary prevention aims at a reduction of recurrence after successful curative treatment of HCC. This review gives a short overview on current strategies in primary, secondary, and tertiary prevention of HCC.

Strategies with a Focus on HBV-Related HCC

Worldwide more than 50% of HCC cases are attributed to chronic HBV infection [6]. A recent systematic review and meta-analysis has revealed a strong correlation of HCC risk in patients with untreated HBV infection with stage of liver disease and age. The incidence rates ranged from 0.07 to 0.42 per 100 person-years in asymptomatic carriers with regional differences between Europe, North America, and Asia, from 0.03 to 0.17 in inactive carriers, from 0.12 to 0.49 in patients with chronic hepatitis, and from 2.03 to 3.37 in patients with decompensated liver cirrhosis [7].

The serum level of HBV DNA is a significant cofactor for the risk of HCC and such are other clinical, viral, demographical, and environmental factors [8].

To prevent the complications of chronic HBV infection, the World Health Organization (WHO) [9] recommends to include hepatitis B vaccination in routine immunization services in all countries. A universal hepatitis B vaccination program has been implemented in 47 of 53 European countries. The first country to routinely vaccinate newborns against HBV was Taiwan who introduced this in 1984. Since then, the rate of HBV infection carriers was significantly reduced, especially in the younger population, which was associated with a significant incidence reduction of HCC in the young by 75% [10, 11]. A drop in the age-standardized incidence rate for HCC after the implementation of vaccination programs has also been demonstrated in other countries, including Singapore, China, and Thailand [12].

Another essential strategy to prevent HCC related to chronic viral hepatitis is testing blood products for HBV and HCV as well as adoption of universal precautions to avoid transmission of blood-borne viruses in healthcare settings [13].

Besides primary prevention of HBV infection, effective antiviral treatment of HBV reduces the risk of HCC. Long-term application of nucleos(t)ide analogs (NA) can result in the improvement of necroinflammation and reversal of fibrosis or even cirrhosis [14]. Most data on the effect of HBV treatment on the risk of HCC comes from studies on interferon therapies and lamivudine [15, 16]. Currently, there is no evidence from prospective randomized controlled trials that show a superiority in terms of HCC prevention with the newer NAs, ente-

cavir and tenofovir disoproxil fumarate, that have a high antiviral potency as well as a high barrier to drug resistance [12]. Risk scores based on demographic (age, sex), clinical (cirrhosis, ALT, albumin, and bilirubin) and virologic characteristics (HBeAg status, HBV DNA) have been developed and predict HCC in Asian chronic hepatitis B patients treated with entecavir, but to a lesser extent in Caucasians [17, 18]. Because intrahepatic cccDNA cannot be eliminated so far, even the new potent drugs are not able to fully eliminate the risk of HCC in chronic hepatitis B-infected patients [19]. Thus, careful surveillance remains mandatory for these patients, particularly in patients with cirrhosis.

In patients that have been diagnosed with HCC related to HBV infection, treatment of HBV in addition to HCC has been demonstrated to significantly improve survival. After curative treatment for HBV-related HCC, controlling viral status seems to be important to prevent HCC recurrence and improve survival. Therapy with interferon and NAs may be useful for preventing HCC recurrence and improving overall survival in patients who have undergone curative resection for HBV-related HCC [20, 21].

Prevention of HCV-Related HCC

HCV is a parenterally transmitted virus. The introduction of anti-HCV testing resulted in a substantial reduction of hepatitis C after transfusion [13]. Nowadays, intravenous drug abuse is the primary cause of HCV transmission. Education programs, needle and syringe exchange programs, safe injecting rooms, and special programs are therefore important measures in the primary prevention of HCV-related HCC but have not satisfactorily shown to be effective. Sexual transmission can be prevented by safe-sex strategies. The outstanding development of new effective therapies against HCV infection will likely have an important impact on HCV-related HCC. Successful treatment of the infection slows liver disease progression and may reduce the risk of cirrhosis and HCC. A meta-analysis of observational studies revealed that sustained virological response is associated with a significantly reduced risk for HCC [relative risk for all persons, 0.24 (95% CI 0.18–0.31)] [5, 22]. With the new interferon-free therapies of HCV infection applying new direct-acting antiviral agents, sustained virological response rates of up to 100% after 12 weeks have been reported in clinical trials irrespective of the genotype and have already been confirmed in real-world settings [23, 24–26]. Nevertheless, also after an effective HCV infection treatment, HCC still develops in some of these patients, especially in the setting of cirrhosis, although it will occur with less likelihood (HR 0.25 in prospective studies) [27]. It is still not clear, however, how successfully anti-HCV therapy will impact on liver fibrosis in the long term and which parameters are useful to identify patients at risk to develop HCC even after HCV clearance [28, 29]. Remarkably, fewer than 20% of infected patients receive treatment of HCV infection in the US and Europe, mostly because patients are not aware of the infection [5]. Hence, this rather low level of treatment penetrance will result in a moderate reduction of HCC incidence attributable to HCV infection in the near future. It cannot be decided yet, if and at what time point patients healed from HCV infection can be dismissed from HCC surveillance and if HCV treatment still has a preventive effect on hepatocarcinogenesis in the stage of advanced liver disease [30]. Several studies have also demonstrated a beneficial effect in term of preventing HCC recurrence in patients after curative resection of HCC in HCV-related liver disease by eradication of HCV. Most of these studies applied interferon [31]. In contrast, it has been demonstrated in a small study that HCV eradication with antiviral agents in patients who have undergone curative treatment of HCC in advance is associated with high recurrence rates of HCC. It is hypothesized that disruption of immune surveillance may facilitate the emergence of metastatic clones [32].

Chronic ALD and HCC

In the Western world, chronic ALD has become one of the leading risk factors for HCC with the special challenge that these patients are frequently missed by surveillance programs, resulting in advanced tumor stages at the time of diagnosis [33–35]. Early diagnosis of ALD is important to encourage alcohol abstinence, minimize the progression of liver fibrosis, and manage cirrhosis-related complications including HCC [36]. The annual HCC rate among patients with Child-Pugh Class A or B alcoholic cirrhosis is about 2.5% [37]. Curing ALD by total abstinence is a challenge. However, a meta-analysis indicates that the risk of hepatic cancer actually decreases after giving up alcohol by 6–7% a year. An estimated period of 23 years is necessary after giving up drinking, i.e. a correspondingly high 95% CI period of 14–70 years, in order that the risk of hepatic cancer becomes the same as that of teetotalers [38, 39].

Options in Prevention of NASH-Associated HCC and HCC Associated with Metabolic Risk Factors

The pathogenesis of HCC in NAFLD is multifactorial involving obesity-mediated mechanisms leading to low-grade chronic inflammation. HCC risk is increased in obesity and diabetes, which constitute two major risk factors for NAFLD [40]. Even in the absence of cirrhosis, a progression from NASH to HCC has been reported [41, 42]. Weight reduction, e.g. by bariatric surgery, has been demonstrated to improve liver fibrosis [43, 44]. Physical activity can improve hepatic steatosis and metabolic indices even without weight loss [44, 45]. Whether this already lowers the risk for HCC has not been sufficiently addressed in clinical studies so far. Targeting the obesity-related inflammation and improvement of insulin resistance with the aim of chemoprevention of hepatocarcinogenesis is in the focus of current research [46, 47]. In diabetics, the use of metformin is associated with a reduced incidence of HCC [48–50], with an odds ratio of 0.30 in a meta-analysis [51]. In addition, the intake of statins reduces the risk of HCC (OR 0.63) in observational studies [52, 53]. There is evidence from early studies pointing at the possibility that treatment with a caspase inhibitor might improve liver histology in NASH [54, 55]. Obeticholic acid, a potent activator of the farnesoid X nuclear receptor, improved the histological features of NASH, but its long-term benefits and safety need further evaluation as well as its preventive effects on hepatocarcinogenesis [56].

Other Causes of Chronic Liver Disease

Hereditary hemochromatosis is a frequent autosomal recessive disorder with frequencies of homozygosity for the most common mutation C282Y reaching up to 1 in 200 and with a disease penetrance ranging from 10 to 60% [57]. In these patients, the presence of cirrhosis is not a prerequisite for HCC development, but early diagnosis and sufficient treatment of iron overload reduces the risk for HCC in these patients [58].

In less developed countries, aflatoxin exposition significantly contributes to the burden of HCC. Preventive measures include public health strategies aiming at a reduction of aflatoxin exposure, including agricultural strategies, methods to reduce humidity and fungal growth, and pharmacological interventions to attenuate the toxicological consequences of unavoidable aflatoxin exposure [57, 59].

Conclusion

The epidemiology of HCC has significantly changed throughout the past decade and will continue to change in the future as a consequence of effective primary prevention and treatment of virus-related liver diseases. However, other risk factors for HCC are constantly on the rise, including ALD and NAFLD. It will be one of the major challenges to improve awareness for patients at risk for HCC development even in the absence of cirrhosis and develop efficient and effective monitoring and intervention strategies to prevent HCC.

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